PATENT
Docket No. 219002029000

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Tami M. Procopio

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In the application of:

Babu J. MAVUNKEL, *et al.*

Serial No.: 09/575,060

Filing Date: 19 May 2000

For: INDOLE-TYPE DERIVATIVES AS INHIBITORS OF p38 KINASE

Examiner: Celia C. Chang

Group Art Unit: 1625

BRIEF ON APPEAL

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants submit herewith, **in triplicate**, their Brief on Appeal in the above-referenced application. A Notice of Appeal was filed on 28 February 2003, setting a date for filing of the Brief of 28 April 2003. A petition for an extension of time of one (1) month until 28 May 2003 is attached along with the required fee. According to the final rejection, claims 1-6, 9, 11-12, 16-27, 29-33, 36-37 and 39 were rejected and appellants appeal the rejection of these claims. Claims 22-28, 34-35 and 45-84 were objected to as dependent on rejected claims but otherwise considered allowable. Claims 40 and 41 were withdrawn from consideration. In accordance

with 37 C.F.R. § 1.192, this Brief, along with the Appendix, is filed **in triplicate** and is accompanied by the required fee.

1. Real Party in Interest

The Real Party in Interest of this application is Scios, Inc., the assignee.

2. Related Appeals and Interferences

No other appeals or interferences that would directly affect or be directly affected by or have a bearing on the Board's decision in this Appeal are known to the appellants, the appellants' legal representative, or the assignee.

3. Status of Claims

The application was filed with 44 claims. Claims 7-8, 10, 13-15, 38 and 43-44 have been canceled; claims 40-41 were withdrawn from consideration. Claims 45-84 were added in a response to a first Office action filed 11 February 2002. Thus, claims 1-6, 9, 11-12, 16-42 and 45-84 are still pending; claims 1-6, 9, 11-12, 16-21, 29-33, 36-37 and 39 stand rejected; claims 22-28, 34-35 and 45-84 are objected to. Claims 40-41 are still pending but withdrawn from consideration. The disposition of claim 42 is not entirely clear, but it does not appear to be rejected.

In the pending claims remaining, claim 1 has been amended twice, once in response to a Restriction Requirement and once in response to the first Office action; claims 2-6 are as originally filed; claim 9 was amended in response to the first Office action; claims 11-12 are as originally filed; claims 16-17 were amended in response to the first Office action; claims 18-29 stand as originally filed. Claim 30 was amended in response to the first Office action and claims 31-42 are as originally filed; claims 45-84 were added in response to the first Office action - claims 45-70 in a response initially filed and claims 71-84 in a supplementary response.

4. **Status of Amendments**

An amendment proposed to claim 1 after final rejection was not entered according to an Advisory Action mailed 18 February 2003.

5. **Summary of the Invention**

The invention is directed to a genus of compounds of a specified structural formula as shown in claim 1 which compounds are useful in treating inflammation or proliferative conditions as well as treating conditions associated with cardiac failure and Alzheimer's disease. It is believed that these conditions are mediated by overactivity of p38 α kinase. (See page 3 of the specification, lines 1-25 and page 4, lines 1-20.) Claim 1 as presently pending is a subset of the genus originally proposed partly as a result of a restriction requirement which required limitation to compounds wherein Z^1 as shown on page 3 is N and wherein l and k are both 1. In addition, L^1 and L^2 defined on page 3 simply as linkers are further defined in the claim as presently pending, they are defined on page 6, line 25-page 7, line 11. The dependent claims are limited to various embodiments of the defined substituents.

All pending claims through claim 37 are directed to defined chemical compounds; claim 39 is directed to a pharmaceutical composition, and claims 40-41 (withdrawn from consideration) depend therefrom but require additional therapeutic agents. Claim 42 is directed to a method to treat rheumatoid arthritis using a compound of claim 1. New claims 45-84 are all directed to compounds.

6. **Issues**

One issue which lies at the root of a rejection under 35 U.S.C. § 103 over Takahashi (JP 09/124631), is whether on page 5, line 16, which defines alkylene as $(CH_2)_n$-R, the generic "n" noted in the formula (which obviously mistakenly contains an extra R) would be interpreted

by the ordinarily skilled reader to be one and the same as the "n" defined on page 3 that denotes the number of R^3 substituents in the α ring of formula (1). If the reader were to interpret the "n" on page 5 as clearly intended, then the compounds disclosed in Takahashi would even more clearly differ from the compounds presently claimed.

The second issue is patentability of the rejected claims over the cited documents. The compounds claimed clearly differ from those in the cited document by virtue of the presence of O rather than NR^7 in the β ring of formula (1).

The third issue relates to rejoinder of claims 40-41.

7. Grouping of Claims

Although appellants believe that some claims, such as claims 4-6 require substituents that distance them even farther from Takahashi than, for example, claim 1, because the claims are so clearly not suggested by the cited document, it is considered pointless to attempt to group them.

8. Argument

A. Alkylene and alkenylene are legitimately defined as containing 1-4C.

Claim 1 as presently pending defines L^1 and L^2 as alkylene or alkenylene each having 1-4C. The designation of 1-4C was objected to as new matter on the basis that the definition of "alkylene" on page 5, line 16, was "$(CH_2)_n$-R"; applicants pointed out, apparently without objection, that the "R" was clearly an error. The Examiner takes the position that the "n" in this formula must be the same as the "n" used to define the number of occurrences of R^3 in the α ring of formula (1).

Appellants can only state that the ordinarily skilled artisan, being used to the use of "n" as a generic designation for a number in general as in the "nth degree" or "where x occurs n

times" would interpret "n" in this location as such a generic, meaning some number in general. Certainly the skilled artisan would not interpret "n" in this context as including 0, because then the alkylene would not exist at all. It seems absurd on its face to assume that the "n" used on page 5, line 16, has the same numerical value as that stipulated for "n" in the defined formula (1) of claim 1.

Further, in all locations where substituents, such as alkyl, that are related to alkylene - *i.e.*, the monovalent form rather than the divalent form - are referred to, the number of carbons is 1-4. See, for example, page 9, line 4, page 9, line 23, page 10, line 25. If this specificity is objected to since "alkylene" as 1-4C is not present *in haec verba* in the application, appellants are willing to delete that specificity from the claim language; however, this offer in response to final rejection was refused.

In any event, it is not seen how alkylene or alkenylene can be present and contain less than 1C. If it is present at all, it must have at least one carbon in the chain (actually alkenylene must have at least 2C).

In sum, appellants believe it is apparent that L^1 and L^2 must actually be present in the molecule, and cannot simply be a bond based on the disclosure of the specification.

B. <u>The Rejected Claims Are Not Obvious Over Takashima Even in Combination with Patani.</u>

First, as has been argued extensively, in the compounds of Takashima (JP 09/124631), a phenyl group is linked directly to the nitrogen of a piperazine ring <u>without</u> a linker. Assuming that appellants prevail in their argument above, at least one carbon atom must intervene between Ar and the piperazine ring in the compounds of claim 1. There is no document suggesting that a spaced aromatic moiety from a piperazine ring would be obvious or suggested by compounds

where an Ar is directly linked to the piperazine. For this reason alone, the compounds of formula (1) are not obvious over the cited document.

A second reason that the compounds of formula (1) are not obvious is that there is no equivalent to CA or CR^8A in ring β. The Examiner points to the compound set forth on page 6 of the cited document which has as this substituent CH_2-NH-$NHCOCH_3$. However, the claims specifically require a carbonyl group in this substituent in place of the CH_2 (methylene). The Office cites Patani as putatively showing that CONH and CH_2NH are bioisosteres in Table 48. However, the mere fact that these may be isosteres does not render CONH obvious over CH_2NH_2 since the biological function may be other than steric. C=O is a reactive group; CH_2 is not.

Third, the compounds of the invention are not obvious over Takashima even combined with Patani because *the invention compounds are essentially indole derivatives whereas the compounds of the cited document are benzofurans*. Appellants realize that this could have been pointed out earlier; however, their undersigned representative took the Examiner at her word that Takashima disclosed all the elements of the claims except the linker (meaning Z^2) "has a methylene chain instead of a carbonyl group" (assuming L^2 could be a bond - which it cannot). Had the structure been examined more closely, rather than focusing on the points raised by the Examiner, it would have been evident that the compounds of the cited document are of a different type entirely. The presence of oxygen rather than NR^7 in the counterpart to the α/β ring system clearly defines a different class of compounds.

Thus, for at least three reasons, the compounds of claim 1, and therefore its dependent claims, are not suggested by Takashima even in combination with Patani.

Copies of Takashima and Patani are enclosed as Exhibits B and C.

C. Claims 40-41 should be rejoined.

Appellants are aware that restriction requirements are petitionable; however, the basis for this restriction requirement was the asserted unpatentability of claim 39 from which claims 40 and 41 depend. (Claim 39 is a pharmaceutical composition comprising as active ingredient the compound of claim 1.) Since claim 39 is itself patentable, claims 40 and 41 which depend therefrom and simply require an additional active ingredient must be patentable as well and there is no reason to judge them separately. Accordingly, appellants request that these claims be rejoined.

CONCLUSION

When properly interpreted, claim 1 requires the presence of linkers between piperazine and both an indole ring system and an aromatic moiety. The documents cited against the rejected claims are benzofuran systems (not indoles) and do not contain a linker between piperazine and an aromatic system. Accordingly, all pending claims are believed allowable and reversal of the outstanding rejection is respectfully requested.

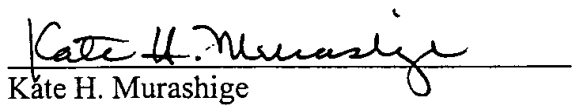
9. Appendix

An Appendix containing a copy of the claims as currently pending is attached.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to Deposit Account No. 03-1952.

Respectfully submitted,

Dated: May 28, 2003

By: 

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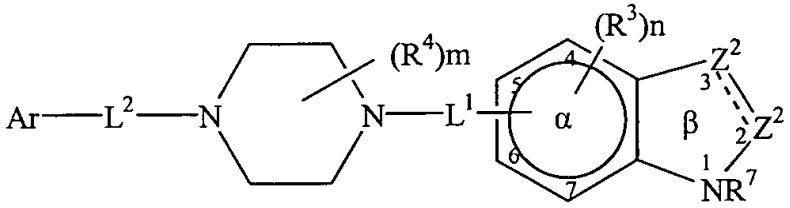
APPENDIX

1. A compound of the formula:



(1)

and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

 represents a single or double bond;

one Z^2 is CA or CR^8A and the other is CR^1, CR^1_2, NR^6 or N wherein each R^1, R^6 and R^8 is independently hydrogen or noninterfering substituent;

A is $-W_i-COX_jY$ wherein Y is COR^2 or an isostere thereof and R^2 is hydrogen or a noninterfering substituent, each of W and X is a spacer of 2-6Å which is substituted or unsubstituted alkylene, alkenylene or alkynylene, and each of i and j is independently 0 or 1;

R^7 is H or is optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, or is SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, NR_2, OR, alkyl-SR, alkyl-SOR, alkyl-SO_2R, alkyl-OCOR, alkyl-COOR, alkyl-CN, alkyl-$CONR_2$, or R_3Si, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof;

each R^3 is independently a noninterfering substituent;

n is 0-3;

each of L^1 and L^2 is independently alkylene (1-4C) or alkenylene (1-4C) optionally substituted with a moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L^1 or L^2 can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or

said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety;

each R^4 is independently a noninterfering substituent;

m is 0-4;

Ar is an aryl group substituted with 0-5 noninterfering substituents, wherein two noninterfering substituents can form a fused ring; and

the distance between the atom of Ar linked to L^2 and the center of the α ring is 4.5-24Å.

2. The compound of claim 1 wherein A is $COXjCOR^2$, and

wherein R^2 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or

wherein R^2 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined; and

X, if present, is alkylene.

3. The compound of claim 1 wherein Y is an isostere of COR^2.

4. The compound of claim 3 wherein Y is tetrazole; 1,2,3-triazole; 1,2,4-triazole; or imidazole.

5. The compound of claim 1 wherein each of i and j is 0.

6. The compound of claim 2 wherein j is 0.

9. The compound of claim 1 wherein R^7 is H, or is optionally substituted alkyl, or acyl.

11. The compound of claim 1 wherein L^1 is CO, CHOH or CH_2.

12. The compound of claim 11 wherein L^1 is CO.

16. The compound of claim 1 wherein L^2 is unsubstituted alkylene and L^1 is CO.

17. The compound of claim 1 wherein L^2 is unsubstituted methylene, methylene substituted with alkyl, or -CH= and L^1 is alkylene or CO.

18. The compound of claim 1 wherein Ar is optionally substituted with 0-5 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

19. The compound of claim 18 wherein Ar is optionally substituted phenyl.

20. The compound of claim 19 wherein said optional substitution is by halo, OR, or alkyl.

21. The compound of claim 20 wherein said phenyl is unsubstituted or has a single substituent.

22. The compound of claim 1 wherein R^4 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR,

$NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^4 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^4 is =O or an oxime, oximeether, oximeester or ketal thereof.

23. The compound of claim 22 wherein each R^4 is halo, OR, or alkyl.

24. The compound of claim 23 wherein m is 0, 1, or 2.

25. The compound of claim 24 wherein m is 2 and both R^4 are alkyl.

26. The compound of claim 1 wherein each R^3 is halo, alkyl, heteroalkyl, OCOR, OR, NRCOR, SR, or NR_2, wherein R is H, alkyl, aryl, or heteroforms thereof.

27. The compound of claim 26 wherein R^3 is halo or alkoxy.

28. The compound of claim 27 wherein n is 0, 1 or 2.

29. The compound of claim 1 wherein L^1 is coupled to the α ring at the 4-, 5- or 6-position.

30. The compound of claim 1 wherein Z^2 at position 3 is CA or CHA.

31. The compound of claim 30 wherein the Z^2 at position 2 is CR^1 or CR^1_2.

32. The compound of claim 31 wherein R^1 is hydrogen, or is alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^1

can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

33. The compound of claim 32 wherein each R^1 is selected from the group consisting of H, alkyl, acyl, aryl, arylalkyl, heteroalkyl, heteroaryl, halo, OR, NR_2, SR, NRCOR, alkyl-OOR, RCO, COOR, and CN, wherein each R is independently H, alkyl, or aryl or heteroforms thereof.

34. The compound of claim 30 wherein Z^2 at position 2 is N or NR^6.

35. The compound of claim 34 wherein R^6 is H, or alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, or is SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

36. The compound of claim 1 wherein  represents a double bond.

37. The compound of claim 1 wherein the distance between the atom on Ar linked to L^2 and the center of the α ring is 7.5-11Å.

39. A pharmaceutical composition for treating conditions characterized by enhanced p38-α activity which composition comprises

a therapeutically effective amount of a compound claim 1 or the pharmaceutically acceptable salts thereof, along with a pharmaceutically acceptable excipient.

42. A method to treat rheumatoid arthritis comprising administering to a subject in need of such treatment a compound of claim 1 or the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.

45. The compound of claim 36, wherein Z^2 at position 3 is CA.

46. The compound of claim 45, wherein Z^2 at position 2 is CR^1.

47. The compound of claim 46, wherein A is $COCOR^2$.

48. The compound of claim 47, wherein R^2 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or

wherein R^2 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined.

49. The compound of claim 48, wherein R^1 is H.

50. The compound of claim 49, wherein n is 0 or 1.

51. The compound of claim 50, wherein Ar is substituted phenyl.

52. The compound of claim 51, wherein L^2 is unsubstituted or substituted alkylene optionally including a heteroatom.

53. The compound of claim 52, wherein L^1 is alkylene or CO.

54. The compound of claim 53, wherein L^2 is methylene and L^1 is CO.

55. The compound of claim 54, wherein n is 1 and R^3 is halo or methoxy.

56. The compound of claim 55, wherein R^7 is H or alkyl.

57. The compound of claim 56, wherein R^7 is methyl.

58. The compound of claim 57, wherein Ar is para-fluorophenyl.

59. The compound of claim 58, wherein R^2 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$ or $NRSO_2NR_2$ wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom containing forms thereof and wherein two R attached to the same atom may form a 3-8 membered ring.

60. The compound of claim 59, wherein R^2 is NR_2 wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom containing forms thereof and wherein two R attached to the same atom may form a 3-8 membered ring.

61. The compound of claim 60, which is selected from the group consisting of compound Nos. 15, 33, 57, 59, 77, 89, 96, and 100 of Table 2, *i.e.*,

1-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2,5-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide;

1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2,5-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide;

1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide;

1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalicamide;

1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N-methyl-glyoxalicamide;

1-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide;

1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalic acid-morpholinamide; and

1-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalic acid-morpholinamide.

62. The compound of claim 60, wherein said compound is compound No. 15 of Table 2, *i.e.*, 1-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2,5-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

63. The compound of claim 60, wherein said compound is compound No. 33 of Table 2, *i.e.*, 1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2,5-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

64. The compound of claim 60, wherein said compound is compound No. 57 of Table 2, *i.e.*, 1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

65. The compound of claim 60, wherein said compound is compound No. 59 of Table 2, *i.e.*, 1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalicamide.

66. The compound of claim 60, wherein said compound is compound No. 77 of Table 2, *i.e.*, 1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N-methyl-glyoxalicamide.

67. The compound of claim 60, wherein said compound is compound No. 89 of Table 2, *i.e.*, 1-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

68. The compound of claim 60, wherein said compound is compound No. 96 of Table 2, *i.e.*, 1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalic acid-morpholinamide.

69. The compound of claim 1, wherein said compound is compound No. 162 of Table 2, *i.e.*, 6-chloro-[4′-fluoro-(4-benzyl-2,5-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

70. The compound of claim 60, wherein said compound is compound No. 100 of Table 2, *i.e.*, 1-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalic acid-morpholinamide.

71. The compound of claim 1, wherein said compound is compound No. 17 of Table 2, *i.e.*, 1-ethoxycarbonyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

72. The compound of claim 1, wherein said compound is compound No. 38 of Table 2, *i.e.*, 1-ethoxycarbonyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

73. The compound of claim 1, wherein said compound is compound No. 45 of Table 2, *i.e.*, 1-t-butoxycarbonyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

74. The compound of claim 1, wherein said compound is compound No. 56 of Table 2, *i.e.*, 1-acetyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

75. The compound of claim 1, wherein said compound is compound No. 60 of Table 2, *i.e.*, 1-acetyl-2-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

76. The compound of claim 1, wherein said compound is compound No. 63 of Table 2, *i.e.*, 1-methoxymethyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

77. The compound of claim 1, wherein said compound is compound No. 92 of Table 2, *i.e.*, 1-methoxymethyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

78. The compound of claim 1, wherein said compound is compound No. 102 of Table 2, *i.e.*, 1-methyl-6-chloro-[4-(1-4'-fluorophenylethyl)piperazinyl]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

79. The compound of claim 1, wherein said compound is compound No. 137 of Table 3, *i.e.*, -methoxy-(4-benzyl piperazinyl)-indole-5-carboxamide-3-glyoxalic acid-methyl ester.

80. The compound of claim 1, wherein said compound is compound No. 138 of Table 3, *i.e.*, [4-(1-phenylethyl)piperazinyl]-indole-5-carboxamide-3-glyoxalic acid methyl ester.

81. The compound of claim 1, wherein said compound is compound No. 152 of Table 3, *i.e.*, (4-benzyl-2R,5S-piperazinyl)-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

82. The compound of claim 1, wherein said compound is compound No. 161 of Table 3, *i.e.*, 6-methoxy-[4'-fluoro-(4-benzyl-2,5-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalic acid-morpholinamide.

83. The compound of claim 1, wherein said compound is compound No. 177 of Table 3, *i.e.*, 6-methoxy-[4'-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

84. The compound of claim 1, wherein said compound is compound No. 180 of Table 3, *i.e.*, (6-methoxy[4-(1-4'-fluorophenylethyl)piperazinyl)-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.